Addressing nutritional requirements in early Alzheimer’s disease: what, why and when?

Laus Broersen, PhD
Senior Neuroscientist
Nutricia Research, Advanced Medical Nutrition
Utrecht, The Netherlands
AD specific nutritional needs for membrane and synapse formation

1. AD-induced compromised nutrient availability
   A. Lower brain nutrient levels
   B. Lower blood nutrient levels
   C. Lower nutrient intake, uptake and metabolism

2. In AD a specific need exists to enhance synapse formation
   A. Patients with AD show lower number of brain synapses
   B. Patients with AD show lower level of neuronal membranes
   C. Membrane and synapse formation dependent on nutrient availability

3. AD specific nutrient requirement to meet the increased demand for synapse formation

4. Souvenaid addresses the nutritional need to support increased synapse formation in patients with AD
Synapse loss is structural basis of functional deficits in AD

Physical Basis of Cognitive Alterations in Alzheimer’s Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Rebecca A. Terry, MD,* Elke Y. Midula, MD,* David R. Selkoe, PhD,+, Helen E. Bowers, PhD,† Eileen Datema, BS,* Rebecca Hill, PhD,* Longzuo A. Huang, MD,* and Nathan Karmaz, MD*″


VIEWPOINT

Alzheimer’s Disease Is a Synaptic Failure

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002

Synapse loss in AD is confirmed in >30 publications
Loss of dendritic spines in AD

4. Conclusions

“... Phospholipids provide an optimal membrane environment for protein interactions, trafficking and function. There is increasing evidence that phospholipid changes occur during pathogenic processes in Alzheimer’s disease. …”
Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis of neuronal membrane

- Uridine
  - Phospholipids
    - Choline
  - Phosphocholine
  - CDP-choline
  - Omega-3 fatty acids
  - Phosphatidylcholine
  - New neuronal membrane

Membranes are main constituents of synapses

- Axon terminal
- Dendritic spine
- Neurite
The Kennedy pathway for biosynthesis neuronal membrane

Dietary precursor control of neural membrane synthesis

Kennedy & Weiss (1956) J Biol Chem


Cansev et al (2005) Brain Res
Dietary precursors can be rate-limiting: Synergy between dietary precursors

Dietary precursors increase membrane dominant structures: Dendritic spines

B-vitamins: cofactors for endogenous production of membrane precursors

CDP-CHOLINE PATHWAY  
de novo phosphatidylcholine synthesis

- UMP
  - UTP
  - CTP
- CHOLINE
- PHOSPHOCHOLINE
- CDP-CHOLINE

PHOSPHATIDYLCHOLINE (enriched in DHA)

- CYSTEINE
  - B6
- PHOSPHATIDYLETHANOLAMINE (enriched in DHA)

PEMT PATHWAY  
de novo choline synthesis

- PHOSPHATIDYLCHOLINE
- SAH
- SAM
- PEMT
- B12
- FA
- B6
- precursor
- cofactor

PEMT = phosphatidylethanolamine-N-methyltransferase
B vitamins increase choline.

B vitamins dose-dependently increase DHA.


Nutritional precursors and cofactors: enhanced availability by Fortasyn Connect

• Synapses are continuously being remodeled
• Synapses are part of the neuronal membrane
• Membranes consist of phospholipids
• Phospholipid synthesis depends on the presence of uridine, choline and DHA
• B-vitamins enhance precursor bioavailability
• Antioxidants protect the neuronal membrane and maintain its integrity, stability and function
Precursors and cofactors enhance synapse formation and function – basic science data

Review

Targeting Synaptic Dysfunction in Alzheimer’s Disease by Administering a Specific Nutrient Combination

Nick van Wijk¹, Laus M. Broersen¹, Martijn C. de Wilde², Robert J.J. Hageman², Martine Groenendijk¹, John W.C. Sijben³ and Patrick J.G.H. Kamphuis¹,*b

¹Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands
²Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

AD risk and nutrient intake

Observational studies suggest a link between Mediterranean diet & AD risk, but data not fully consistent

**Mediterranean diet:**
- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals

Systematic review and meta-analysis on nutrient availability in AD

- According to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines
- Analyses by independent statisticians

Flow Chart Literature Search

Total amount of publications: 4768 (Medline + Embase + Cochrane Central Register of Controlled Trials)

- removed duplicates: 1371

Single publications: 3397
- obvious non-relevant articles on basis of title/abstract/not-English: 2673

Possibly relevant publications on basis of title and abstract: 724

Plasma nutrient status of patients with Alzheimer’s disease: Systematic review and meta-analysis

Sofia Lopes da Silva\textsuperscript{a,b}, Bruno Vellas\textsuperscript{c}, Saskia Elemans\textsuperscript{a}, José Luchsinger\textsuperscript{d}, Patrick Kamphuis\textsuperscript{a,b}, Kristine Yaffe\textsuperscript{e}, John Sijben\textsuperscript{a,*}, Martine Groenendijk\textsuperscript{a}, Theo Stijnen\textsuperscript{f}
Systematic review and meta-analysis of literature: Lower plasma levels of precursors & cofactors in AD

Plasma nutrient status in AD
Meta-analyses, systematic review and observations

*1 Trushina (2013) PLOS
*2 Olde Rikkert (2013) ADPD
Meta-analyses
Lin (2012) JCP
Data on file
Lopes da Silva (2013) Alz Dement
Systematic review
Loef (2011) JAD
Lower nutrient status preceding classic protein energy malnutrition

Epidemiological relate dietary patterns with AD risk

Mi et al (2013) Nutrition
Development of Souvenaid: addressing AD specific requirements

**Stimulating synapse formation requires specific nutrients**

- Uridine (UMP)
- Omega-3 fatty acids
- Phospholipids & Choline
- B-Vitamins
- Antioxidants

**Increased nutritional need cannot be met by the regular diet**

**HYPOTHESIS:** Souvenaid successfully addresses an unmet nutritional need in people with AD by increasing their intake of these dietary precursors and co-factors.
### Prodromal AD
- S-Connect
- Souvenir I
- Souvenir II
- Open Label
- MEG study
- MRS study
- NL-Enigma
- LipiDiDiet

### Mild AD
- WMS-r & ADAS-cog
- MMSE 20-26, drug-naïve

### Moderate AD
- ADAS-cog
- MMSE 14-24, stable on AD drugs
- NTB + EEG
- MMSE ≥ 20, drug-naïve
- Safety + Compliance + NTB
- MEG + EEG + NTB
- MMSE ≥ 20, drug-naïve
- $^{31}$P and $^{1}$H-MRS
- MMSE ≥ 20, drug-naïve
- $^{18}$FDG-PET
- MMSE ≥ 20, drug-naïve

NTB + MRI / CSF
- MMSE ≥ 24, drug-naïve

Souvenir I received funding from NL STW
Souvenir II receives funding from the NL Food & Nutrition Delta project, FND N°10003
LipiDiDiet is funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696
NL-Enigma funded by NWO NIHC project, N°057-13-003.
S-Connect study: mild to moderate AD on AD medication

- Principle investigators: David Bennett and Raj Shah, Rush, Chicago
- Multi-centre (48 sites in the US), randomized, controlled trial
- Intervention 24 weeks
- Primary outcome:
  - ADAS-cog-11

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=262)</th>
<th>Active (n=265)</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>76.9 (8.2)</td>
<td>76.6 (8.2)</td>
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<td>Sex: males (n[%])</td>
<td>127 (48.5%)</td>
<td>126 (47.5%)</td>
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<td>Years of education on top of primary school</td>
<td>6.4 (3.5)</td>
<td>6.7 (3.6)</td>
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<tr>
<td>Total MMSE score</td>
<td>19.3 (3.0)</td>
<td>19.5 (3.2)</td>
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<td>Duration AD since diagnosis (months)</td>
<td>34.9 (29.6)</td>
<td>32.7 (25.0)</td>
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<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>243 (92.7%)</td>
<td>251 (94.7%)</td>
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<tr>
<td>NMDA antagonist</td>
<td>170 (64.9%)</td>
<td>177 (66.8%)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.64 (4.56)</td>
<td>26.19 (4.51)</td>
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No significant effect (p=0.513) during 24 weeks

Souvenir I: Proof of concept study in drug-naive mild AD

- Multi-country (NL, Bel, Ger, UK, US), randomized, controlled trial
- Intervention 12 weeks (+ optional 12 wk extension)
- Co-primary outcomes:
  - WMS-r delayed verbal recall
  - ADAS-cog-13


Significantly more responders after 12 weeks (p=0.021)
Souvenir II study: drug-naive mild AD

- Multi-country (NL, Ger, Bel, Fr, It, Sp), randomized, controlled trial
- Intervention 24 weeks
- Primary outcome: Memory Domain NTB (z-score):
  - RAVLT immediate, delayed, recognition and VPA immediate and delayed

The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer’s Disease: A Randomised Controlled Study

Hanneke de Waal\textsuperscript{1,6}, Cornelis J. Stam\textsuperscript{2}, Marieke M. Lansbergen\textsuperscript{3}, Rico L. Wiegers\textsuperscript{3}, Patrick J. G. H. Kamphuis\textsuperscript{3}, Philip Scheltens\textsuperscript{1}, Fernando Maestu\textsuperscript{4}, Elisabeth C. W. van Straaten\textsuperscript{2,3}

1 Alzheimer Center & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, 2 Department of Clinical Neurophysiology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, 3 Nutricia Research, Utrecht, The Netherlands, 4 Laboratory of Cognitive and Computational Neuroscience, UCM-UPM Center for Biomedical Technology, Madrid, Spain

Plasma phospholipids identify antecedent memory impairment in older adults

Mark Mapstone¹, Amrita K Cheema²,³, Massimo S Fiandaca⁴,⁵, Xiaogang Zhong⁶, Timothy R Mhyre⁵, Linda H MacArthur⁵, William J Hall⁷, Susan G Fisher⁸,¹⁴, Derick R Peterson⁹, James M Haley¹⁰, Michael D Nazar¹¹, Steven A Rich¹², Dan J Berlau¹³,¹⁴, Carrie B Peltz¹³, Ming T Tan⁶, Claudia H Kawas¹³ & Howard J Federoff⁴,⁵

- Mapstone et al. identified a biomarker panel of 10 plasma lipids that can predict conversion from cognitive healthy to MCI/AD within 2-3 years with >90% accuracy
- Changes may reflect the breakdown of neuronal membranes
- Highly publicitized findings

- set of 10 plasma lipids, including 8 phospholipids
- levels are lower in converters and MCI/AD subjects
Souvenaid increases levels of the biomarker phospholipids

- Baseline and 24-week plasma samples from the Souvenir II study
- Drug-naïve patients with very mild AD
- Polar lipid profile

By providing nutrients which normally rate-limit phospholipid synthesis, Souvenaid can:
- modify a biomarker profile reflecting disturbed phospholipid metabolism
- be useful in asymptomatic subjects with plasma lipid biomarker profiles predictive for conversion to AD

5 / 7 measured phospholipids reported by Mapstone significantly increased by Souvenaid

* P<0.001; Souvenaid vs. Control using ANCOVA
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Thank you!